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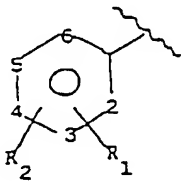
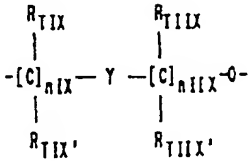


(Ia)



(B)

(57) Abstract

Organic or inorganic salts of compounds of general formula: A – X_1 – $N(O)_z$ for use as medicaments having anti–inflammatory, analgesic and antithrombotic activity, wherein A is $R(COX_u)_t$ wherein t is 0 or 1; u is 0 or 1 and X is O, NH, NR_{1c} wherein R_{1c} us a C_1–C_{10} alkyl and R is, for example, (Ia) wherein R_1 is acetoxy, preferably in ortho position with respect to –CO– and R_2 is hydrogen or acetylsalicylsalicylic acid derivatives; and X_1 is the formula (B), Y being a ring containing at least one salified nitrogen atom.

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NITROXYDERIVATIVES HAVING ANTIINFLAMMATORY, ANALGESIC AND ANTITHROMBOTIC ACTIVITY

* * * * * *

The present invention relates to new products having anti-inflammatory, analgesic and antithrombotic activity.

Specifically it relates to cyclo-oxygenase (COX) inhibitors.

It is known that the anti-inflammatory and antithrombotic efficacy of NSAIDs (Non steroid antiinflammatory drugs), also known as FANS (non steroid antiinflammatory drugs), but especially their tolerability, seem to be considerably affected by their inhibitory activity of the cyclo-oxygenase (COX) both in the inflammatory site and in the healthy tissue. See for example FASEB Journal 1, 89, 1987; Bioch. Biophys. Acta 1083, 1, 1991. The drawback of these products is that they are toxic, as already described in USP 5,861,426.

Nitroderivative compounds, described in said patent, are also known, have an high efficacy in the cyclooxygenase inhibition and a low toxicity. However these compounds show some drawbacks connected to the chemical-physical and structural characteristics of the molecules themselves, these latter being highly lipophilic and therefore having a poor solubility in water. It is well known that the solubilization process is decisive for absorption and interaction with the

effector. The poor solubility generally involves a variable and unpredictable efficacy whereby it is difficult to set a correct posology. In practice it is necessary to administer higher doses in order to contain the above mentioned variabilities. The drawback is the risks of a higher incidence of side effects. Another disadvantage bound to the poor solubility of the nitroderivatives of said patent application is that they are difficult to be formulated. It is well known that the solubility in water of a molecule is one of the most important properties affecting the pharmacokinetic and pharmacodynamic processes. For example for parenteral administration, particularly by intravenous route, drugs must be formulated in solutions. In order to increase solubility, when it is unsatisfactory for these uses, the choice of suitable solvents and/or excipients is therefore critical, for example, among the latter, surfactants, etc., can be mentioned. This can lead to drawbacks from the toxicological point of view connected to the excipient tolerability; besides there are other drawbacks for example in the intravenous formulation which, as well known, must not cause haemolysis or incompatibility with blood constituents. Besides it is necessary to notice that it is well known that surfactants and apolar solvents can be irritant. See for example J. Pharm. Science 72, 1014, 1983.

Experiments carried out by the Applicant, wherein 0.1%

Tween 80 and 1% dimethylsulphoxide have been used to suspend the nitroxy derivatives of the antiinflammatory compounds described in the patent application WO 95/30641 have shown that these substances were irritant towards the gastric mucous membrane.

It has unexpectedly been found that the derivatives of the present invention, differently from the above mentioned compounds of the prior art, can be solubilized without using the substances commonly used in the pharmaceutical technique to obtain solutions or suspensions, maintaining or even improving the activity of the prior art nitroxy derivatives. A further advantage of the compounds of the present invention is that it is possible to avoid adding to the formulation the excipients, such as for example those above mentioned, which cause or can induce irritant effects.

The antiinflammatory products described in the present application have an high cyclo-oxygenase inhibiting activity combined with low toxicity and pharmacokinetic good responses, and have furthermore a better systemic absorption degree.

This is quite surprising and unexpected since the factors affecting the FANS antiinflammatory and antithrombotic efficacy depend on various parameters whereby it is not possible to foresee a priori the pharmacokinetics, for example the absorbed product fraction, the pharmacodynamic activity, the toxicity and the COX inhibiting properties and most of

all, no assumptions can be made to predict or limit the response variability.

An object of the present invention are compounds or organic or inorganic salts of compounds of general formula:

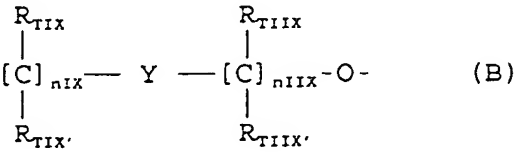
$$A - X_1 - N(O)_z$$

for use as medicaments, specifically as antiinflammatory and antithrombotic agents, wherein:

z is an integer and is 1 or 2, preferably 2;

A = $R(COX_u)_t$ and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched C_1-C_{10} alkyl;

X_1 =  (B)

wherein:

nIX is an integer between 0 and 3 , preferably 1;

nIIX is an integer between 1 and 3, preferably 1;

R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other, are H or linear or branched C_1-C_4 alkyl; preferably R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$ are H;

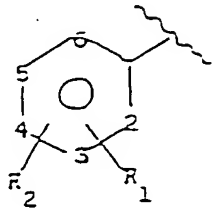
Y is a ring containing at least one salifiable nitrogen atom; preferably Y is an heterocyclic ring, saturated or unsaturated or aromatic, having preferably 5 or 6 atoms and containing at least one or two nitrogen atoms, preferably one or two

nitrogen atoms;

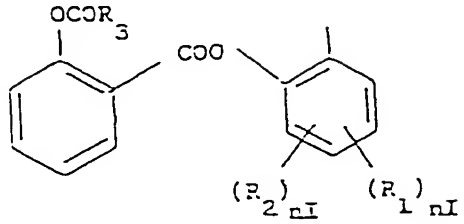
R is selected from the following groups:

Group I) wherein t = 1 and u = 1

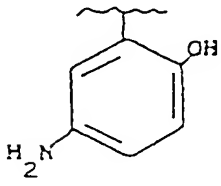
Ia)

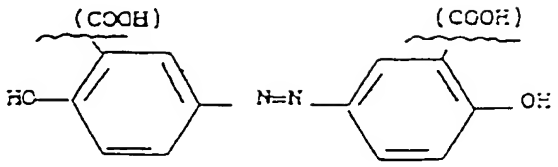


Ib)

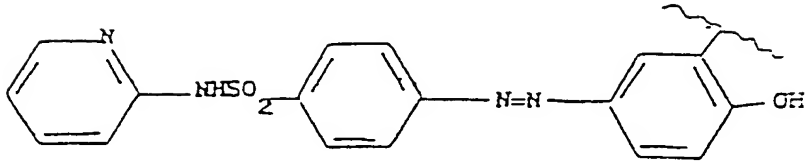


Ic)





IC_1) IC_2)



IC_3)

wherein:

R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3-C_5 alkyl, or the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or totally hydrogenated, containing one or more hetero-atoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, a linear or when possible branched C_1-C_4 alkyl, a linear or when possible branched C_1-C_4 alkoxyl; a linear or when possible branched C_1-C_4 perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di-(C_{1-4}) alkylamino;

nI is an integer 0 or 1;

preferably in the compounds of formula Ia) X is equal to O or NH, R_1 is acetoxy, preferably in ortho position with respect to -CO-, R_2 is hydrogen; in X_1 $R_{TIX} = R_{TIX'} = R_{TIIX} = R_{TIIX'} = H$, $n_{IX} = n_{IIX} = 1$ and Y is an aromatic ring having 6 atoms, containing one nitrogen atom, said aromatic ring having the two free valences in position 2 and 6.

Preferably in the compounds of formula Ib) $R_3 = CH_3$, nI = 0, X is equal to O, X_1 is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid.

The compounds Ic) of formula Ic_1) are the 5-amino salicylic acid derivatives (5-amino-2-hydroxybenzoic acid), for example mesalamine, when the valence is saturated with -COOH.

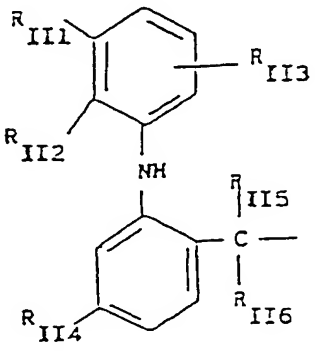
In the compounds of formula Ic_2) at least one of the two carboxyl groups is reacted for obtaining the invention compounds. When both carboxyl groups react, bifunctional compounds are obtained. When the two valences are saturated with -COOH, the compound known as olsalazine is obtained. When one of the two valences instead of -COOH is saturated with $-CONHCH_2-CH_2-COOH$, the compound is known as balsalazide, wherein -OH which is in ortho position in the same aromatic ring is substituted with H.

The compounds of formula IC_3) are known as sulphalazine: 2-hydroxy-5-[(2-pyridinylamino)sulphonyl]phenyl]azo] benzoic acid when the free valence is saturated with -COOH.

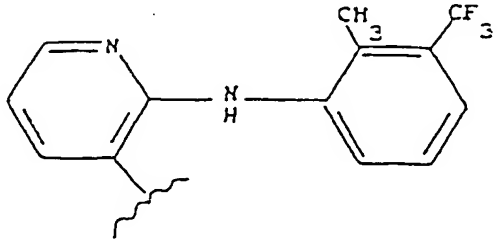
The preferred Ic) compounds have X = O and u = 1;

Group II) wherein t = 1, u = 1

IIa)



IIb)



wherein:

R_{II5} is H, a linear or branched when possible C_1-C_3 alkyl;

R_{II6} has the same meaning as R_{II5}, or when R_{II5} is H it may be benzyl;

R_{II1}, R_{II2} and R_{III3} can independently be hydrogen, a linear or when possible branched C_1-C_6 alkyl or a linear or when possible branched C_1-C_6 alkoxy, or Cl, F, Br;

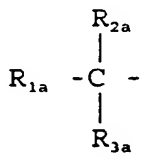
R_{II4} is R_{II1} or bromine;

the compounds wherein R_{II1}, R_{II4} are hydrogen and R_{II2} and R_{II3} are chlorine in ortho position with respect to NH are preferred;

R_{II5} and R_{II6} are H, X is equal to O, and X_1 is as above defined for the compounds of formula Ia);

IIb) is the residue of the 2-[(2-methyl-3-(trifluoro-methyl)phenyl]amino]-3-pyridincarboxylic] acid and when the -COOH group is present the compound is known as flunixin;

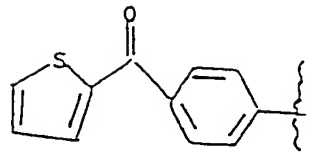
Group III) wherein t = 1, u = 1 and R is



wherein:

R_{2a} and R_{3a} are H, a linear or when possible branched, substituted or non-substituted, C_1-C_{12} alkyl or allyl, with the proviso that when one of the two is allyl, the other is H; preferably R_{2a} is H, C_1-C_4 alkyl, R_{3a} is H;

R_{1a} is selected from



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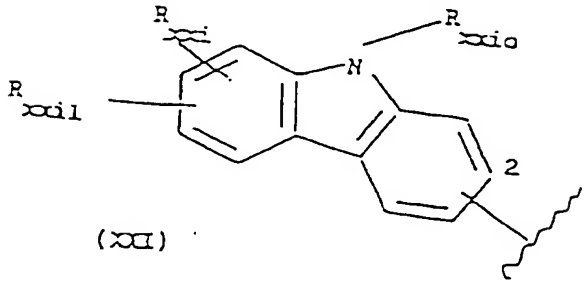
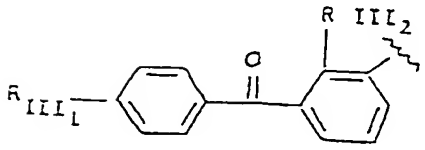


(XXI)



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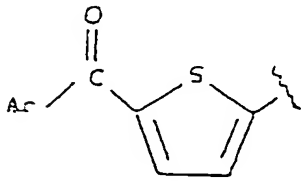

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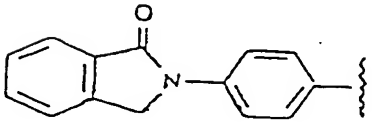

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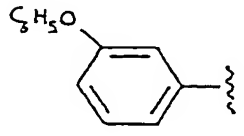

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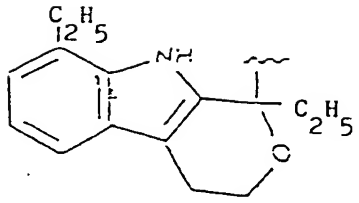
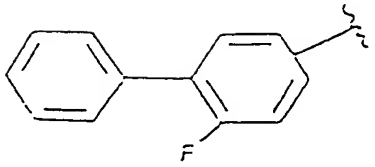


(VIII)



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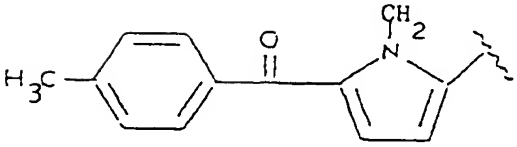

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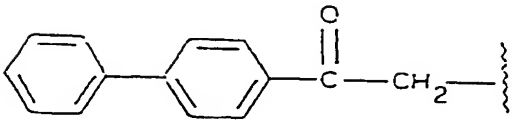
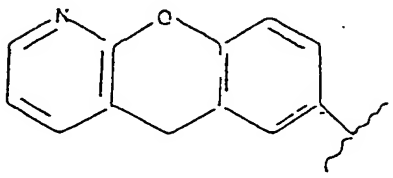
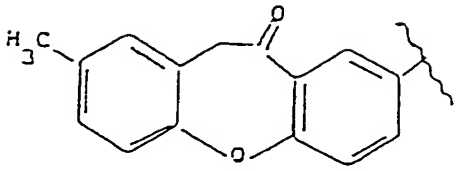


(III)

IIID) R_{1a} corresponds to the following formulas:



(IIIa)



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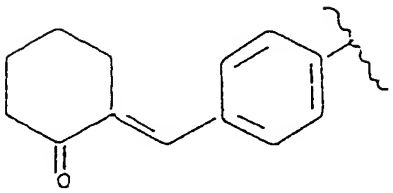

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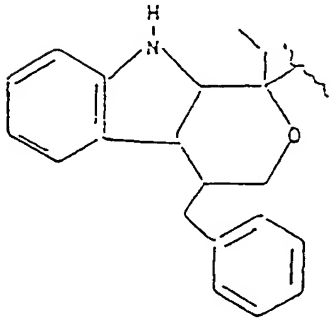

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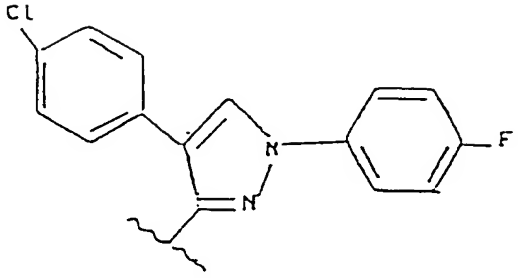

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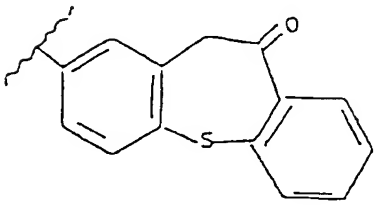

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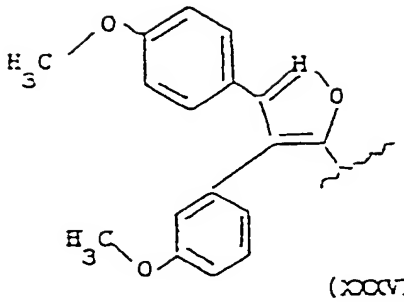

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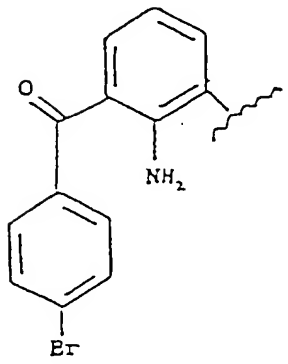


(XII)

wherein the meanings are the following:

when R_{1a} is as defined in formula (IV), Ketoprofen residue:

R_{III1} is H, SR_{III3} wherein R_{III3} contains from 1 to 4 C atoms, linear or branched when possible;

R_{III2} is H, hydroxy;

preferred are the compounds wherein R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, X = O;

when R_{1a} is as defined in formula (XXI), carprofen residue:

R_{xxio} is H, a linear or when possible branched alkyl having from 1 to 6 C atoms, a C_1-C_6 alkoxycarbonyl bound to a C_1-C_6 alkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkanoyl, optionally substituted with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;

R_{xxi} is H, halogen, hydroxy, CN, C_1-C_6 alkyl optionally

containing OH groups, C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xxi2} wherein R_{xxi2} is C_1-C_6 alkyl; C_1-C_3 perfluoroalkyl; C_1-C_6 carboxyalkyl optionally containing OH groups, NO_2, amino; sulphamoyl, di-alkyl sulphamoyl with C_1-C_6 alkyl, or difluoroalkylsulphonyl with C_1-C_3 alkyl;

R_{xxi1} is halogen, CN, C_1-C_6 alkyl containing one or more OH groups, C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy, SR_{xxi3} being R_{xxi3} as above defined, C_1-C_3 perfluoroalkyl, hydroxy, C_1-C_6 carboxyalkyl, NO_2, amino, mono- or di-alkyl-amino C_1-C_6; sulphamoyl, di-alkyl sulphamoyl C_1-C_6, or di-fluoroalkyklsulphamoyl as above defined; or R_{xxi} together with R_{xxi1} is a C_1-C_6 alkylene dioxy;

preferred are the compounds wherein R_{xxio} is H, the linking bridge is in position 2, R_{xxi} is H, R_{xxi1} is chlorine and is in para position with respect to nitrogen;

R_{3a} is H, R_{2a} is methyl and X is O;

when R_{1a} is as defined in the formula (XXXV), residue of the tiaprofenic acid:

Ar is phenyl, hydroxyphenyl optionally mono- or poly-substituted with halogen, alkanoyl and C_1-C_6 alkoxy, C_1-C_6 trialkyl, preferably C_1-C_3, cyclopentyl, cyclohexyl cycloheptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;

the preferred compounds of (XXXV) are those wherein Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O;

when R_{1a} is as defined in formula (II), suprofen residue, of which the preferred one has been shown, wherein R_{3a} is H, R_{2a} is methyl and X = O, as described and obtained in USP 4,035,376 herein incorporated by reference;

when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when R_{2a} = H and R_{3a} = CH_3;

of indobufen when R_{2a} is equal to H and R_{3a} = C_2H_5; X = O, as described and obtained according to USP 3,997,669 herein incorporated by reference;

when R_{1a} is as defined in formula (VIII), R is the residue of etodolac when R_{2a} = R_{3a} = H and X = O, as described in and obtained according to USP 3,843,681 herein incorporated by reference;

when R_{1a} is as defined in formula (VII), R is the residue of fenoprofen when R_{3a} = H, R_{2a} = CH_3 and X = O, as described in and obtained according to USP 3,600,437 herein incorporated by reference;

when R_{1a} is as defined in formula (III), R is the residue of fenbufen when R_{2a} = R_{3a} = H and X = O, as described in and obtained according to USP 3,784,701 herein incorporated by reference;

when R_{1a} is as defined in formula (IX), R is the residue of flurbiprofen when R_{3a} = H, R_{2a} = CH_3, X = O;

when R_{1a} is as defined in formula (X) R is the residue of tolmetin when R_{2a} = R_{3a} = H, X = O, as described in and

obtained according to FR 1,574,570 herein incorporated by reference.

In the group IIID) R_{1a} corresponds to the following formulas: -

IIIa), when R_{2a} = H and R_{3a} = CH_3 the residue of pranoprofen is obtained: α-methyl-5H-[1]benzopyrano-[2,3-b]pyridin-7-acetic acid; in the preferred compound R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O:

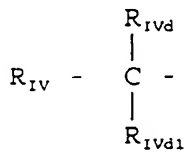
- (XXX), when R_{2a} = H and R_{3a} = CH_3 the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid; in the preferred compound R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O.
- (XXXI), when R_{2a} = H and R_{3a} = CH_3, R is the radical of the compound CS-670: 2-[4-(2-oxo-1-cyclohexylidene methyl) phenyl]propionic acid; the preferred compound has R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- (XXXII), when R_{2a} = R_{3a} = H the Pemedolac residue is obtained; the preferred compound has R_{2a} = R_{3a} = H, u = 1 and X = O;
- (XXXIII), when R_{2a} = R_{3a} = H the pirazolac residue is obtained: derivatives of the 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolic acid;

  the preferred compounds have R_{2a} = R_{3a} = H, u = 1 and X = O.
- (XXXVI), when R_{2a} = H, R_{3a} = CH_3, the zaltoprofen residue is obtained; when the residue is saturated with an hydroxyl or aminic group, or with the carboxylic function

the compounds are known as dibenzothiepin derivatives; in the preferred compounds R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O.

- (XXXVII), when R_{2a} = R_{3a} = H the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid when the residue is CH_2-COOH; in the preferred compounds R_{2a} = R_{3a} = H, t = 1 and X = O;
- (XII), when R_{2a} = R_{3a} = H the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid; the preferred compounds have u = 1, t = 1, X = O, R_{2a} = R_{3a} = H; or t = 0;

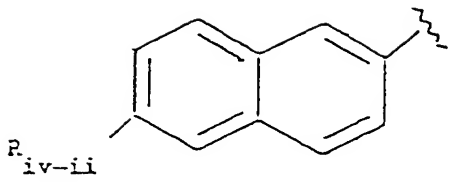
In the group IV) wherein t = 1, u = 1, R is



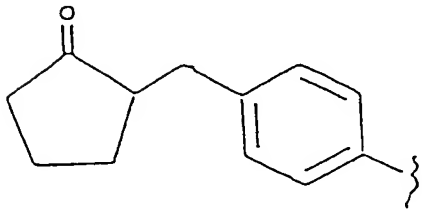
wherein:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched when possible alkyl from C_1 to C_6 , preferably C_1 and C_2, or difluoroalkyl with the alkyl having from 1 to 6 C atoms, C_1 is preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

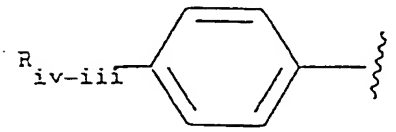
R_{IV} has the following meaning:



(II)



(X)



(III)

wherein the compounds of group IV) have the following meanings: in formula (II)

R_{iv-ii} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_7 alkoxymethyl, C_1-C_3 trifluoroalkyl, vinyl, ethynyl, halogen, C_1-C_6 alkoxy, difluoroalkoxy, with the C_1-C_7 alkyl, C_1-C_7 alkoxymethyloxy, alkylthiomethyloxy with the C_1-C_7 alkyl, alkyl methylthio with the C_1-C_7 alkyl, cyano, difluoromethylthio, phenyl- or phenylalkyl substituted with the C_1-C_8 alkyl; preferably R_{iv-ii} is CH_3O-, R_{IVd} is H and R_{IVd1} is CH_3, and is known as naproxen residue;

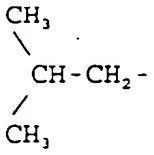
X = O and X_1 is as above defined for Ia);

in formula (X), of which the loxoprofen residue has been shown, described in USP 4,161,538 herein incorporated by reference, the compounds are preferred wherein R_{IVd} is H and R_{IVd1} is CH_3, X = O and X_1 is as above defined for Ia);

in formula (III):

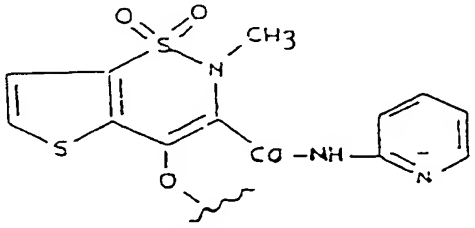
R_{iv-iii} is a C_2-C_5 alkyl, optionally branched when possible, C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, cycloalkyl from 5 to 7 C atoms, optionally substituted in position 1 with a C_1-C_2 alkyl;

the compound in which R_{iv-iii} is

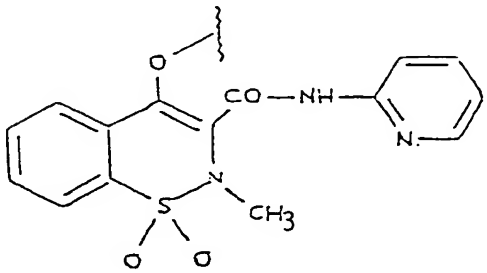


and R_{IVd} = H, R_{IVd1} is CH_3, is preferred, a compound known as ibuprofen residue; X = O and X_1 is as above defined for Ia);

Group V)



(VII)



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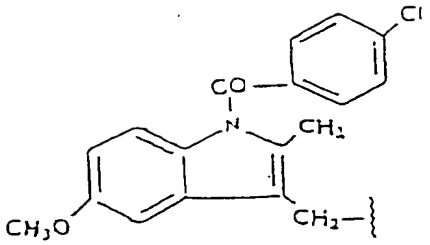

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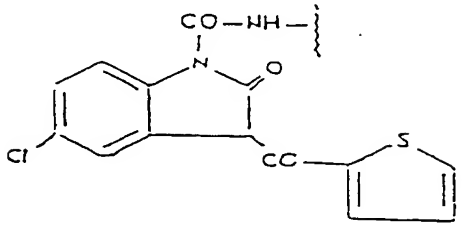

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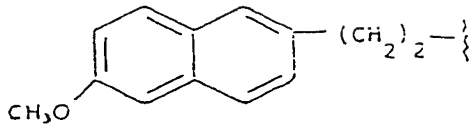

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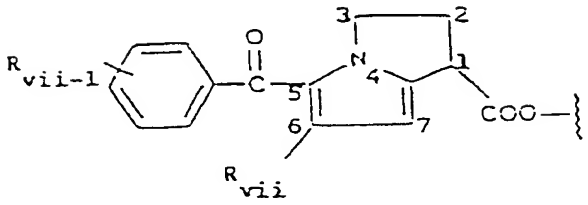
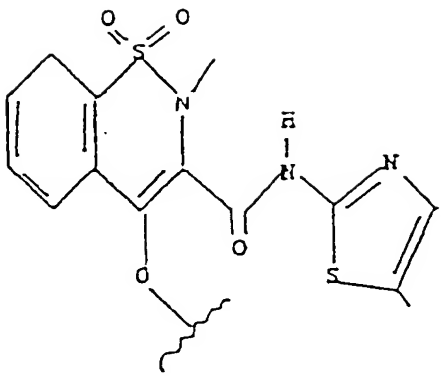
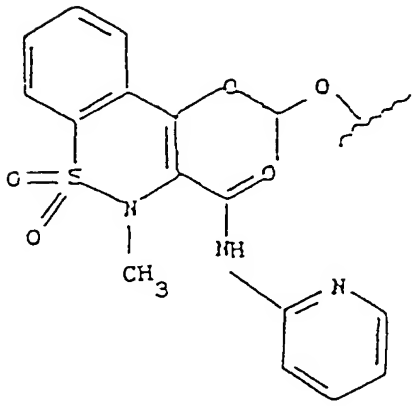


(II)

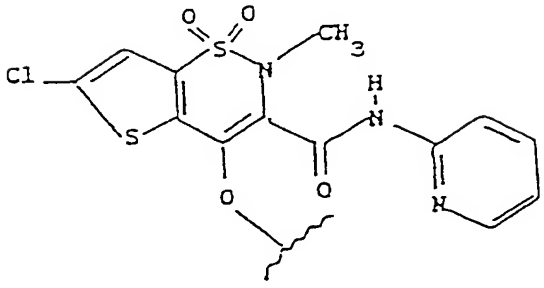
Group VE)



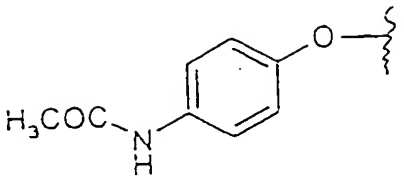
(X)



(XI)



(XIII)



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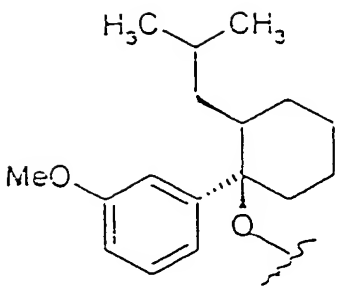


(XXXXI)

In group V), the compounds have the following meanings:

when R is the formula (II),

R_{vii} is H or a linear or branched when possible C_1-C_4 alkyl;

R_{vii-1} is R_{vii}, or a linear or branched when possible C_1-C_4 alkoxy; Cl, F, Br; the position of R_{vii-1} being ortho, or meta, or para;

the residue of the known Ketorolac is preferred, wherein R_{vii} and R_{vii-1} are H, and A = R (A being the group of the formula $A\text{-}X_1\text{-}NO_2$) and t = 0;

when R is the formula (V),

of which the residue of the known tenidap has been mentioned, as described and obtained in USP 4,556,672 herein incorporated by reference;

in these compounds of formula (V) A = R and t = 0,

when R is the formula (VII),

of which the residue of the known tenoxicam has been mentioned, A is RCO, t = 1 u = 0 or A is R and t = 0, as

described and obtained in DE 2,537,070 herein incorporated by reference;

when R is the formula (IX),

wherein A = R and t = 0, or A = RCO with t = 1 and u = 0, the residue of the known piroxicam has been indicated, as described and obtained in USP 3,591,584 herein incorporated by reference;

when R is the formula (III)

wherein A = RCOO, t = 1 and u = 0 or 1; or t =0 and A= R, of which the residue of the known nabumetone has been indicated, as described and obtained in USP 4,061,779 herein incorporated by reference;

when R is the formula (IV)

wherein A = RCOO, t = 1 and u = 1,

of which the indomethacin residue has been indicated, as described and obtained in USP 3,161,654 herein incorporated by reference;

when R is the formula (X), the residue X is known as meloxicam;

the preferred compounds are those wherein A = RCO, t = 1 and u = 0;

when R is the formula (XI) the residue is known as ampiroxicam when the end group is $-CH(CH_3)OCOC_2H_5$; the preferred compounds have A = RCO, t = 1 and u = 0;

when R is the formula (XIII) and the valence is saturated with

H

the residue derives from lornoxicam; the preferred compounds have A = RCO, t = 1 and u = 0;

when R is the formula (XXXX) and the valence is saturated with H

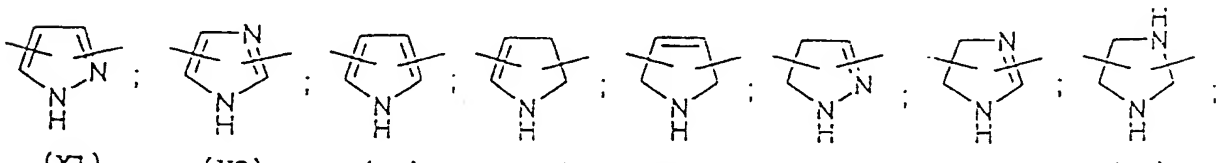
the compound known as paracetamol is obtained, as described and obtained in USP 2,998,450 herein incorporated by reference;

when R is the formula (XXXXI) and the valence is saturated with H

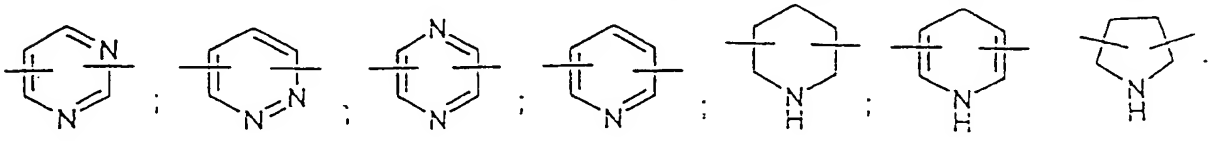
the compound known as Tramadol is obtained, as described and obtained in USP 3,652,589;

the preferred compounds according to the present invention obtainable with the radicals corresponding to the formulas (XXXX) and (XXXXI) have A= RCO, t = 1 and u = 0.

Y in the above mentioned X_1 formula contains one or two nitrogen atoms in the ring, and preferably selected from the following:



(Y1) (Y2) (Y3) (Y4) (Y5) (Y6) (Y7) (Y8)



(Y9) (Y10) (Y11) (Y12) (Y13) (Y14) (Y15)

The preferred of Y is Y12 (pyridyl) substituted in position 2 and 6. The bonds can be also in non symmetric position, for example Y12 (pyridyl) can be substituted also in position 2 and 3; Y1 (pyrazol) may be 3,5-disubstituted.

The X_1 precursors, wherein the oxygen free valence is saturated with H and the free valence of the end carbon is saturated either with a carboxylic or hydroxyl group, are commercially available products or are obtainable with methods known in the prior art.

The compounds containing R of group I) of the type Ia) are described in the patent WO 92/01668 wherein the preparation methods are also described. This patent is herein incorporated by reference. The type Ib) compounds are for example prepared by using the method shown in The Merck Index, XI ed., 1989, pag. 16, No. 95 for the residue of the acetylsalicylsalicylic acid. The changes of the compounds of formula Ib) may be obtained by applying the processes mentioned in the patent WO 92/01668.

Compounds Ic) of the Ic_1) class, in which the radical is a 5-amino salicylic acid derivative (5-amino-2-hydroxybenzoic acid) known as mesalamine, when the starting radical contains -COOH, are prepared by reduction of the m-nitrobenzoic acid with Zn powder and HCl (see H. Weil et al., Ber. 55B, 2664 (1922)), or by electrolytic reduction: Le Guyader, Peltier, Compt. Rend. 253, 2544 (1961). These publications are herein

incorporated by reference.

The starting radical Ic_2), when it contains -COOH, is known as olsalazine: 3,3'-azabis(6-hydroxybenzoic) acid; and it is prepared according to EP 36,636 or USP 4,528,367, both herein incorporated by reference.

The Ic_3) compounds are prepared according to USP 2,396,145 herein incorporated by reference.

Equivalent compounds to Ic_1), Ic_2) and Ic_3) contain the substituents mentioned in the above references.

The compounds wherein R is of the group II) are described in the patents WO 94/04484 and USP 3,558,690 wherein the preparation methods are also described. These patents are herein incorporated by reference.

The starting compound of IIb), when the valence is saturated with -COOH (flunixin), is obtained according to USP 3,337,570 and USP 3,689,653, both herein incorporated by reference. The compounds containing the substituents mentioned in the previous patents are equivalent to flunixin.

The compounds wherein R is of group III) are described and obtained with the processes mentioned in the following patents:

patent application PCT/EP/93 03193; for the compounds of formula (IV) see also USP 3,641,127; for the compounds of formula (XXI) see also USP 3,896,145; for the compounds of formula (IX) residue of flurbiprofen see also USP 3,755,427; for the

compounds of formula (II) see also USP 4,035,376; for the compounds of formula (VI) see also USP 3,997,669; for the compounds of formula (VIII) see also USP 3,843,681; for the compounds of formula (VII) see also USP 3,600,437; for the compounds of formula (III) see also USP 3,784,701.
All the above mentioned patents are herein incorporated by reference.

The processes for preparing the compounds of class IIID) are the following:

The residue IIIa) is obtained by preparing the acid compound according to USP 3,931,205, the valence is saturated with $-CH(CH_3)-COOH$. The compounds containing the substituents mentioned in the above patent are equivalent to pranoprofen. The residue (XXX) is prepared through the compound with the $-CH(CH_3)-COOH$ group (bermoprofen) according to USP 4,238,620 herein incorporated by reference. Other equivalent products are described in the above mentioned patent.

The residue (XXXI) is prepared starting from the corresponding $-CH(CH_3)-COOH$ acid according to USP 4,254,274. Equivalent compounds are described in the same patent.

The residue (XXXII) is prepared according to EP 238,226 herein incorporated by reference, when the valence is saturated with $-CH_2-COOH$. Equivalent products are reported in said patents as substituted 1,3,4,9 tetrahydropyrane [3,4-b] indol-1-acetic acids.

The residue (XXXIII) is prepared from pirazolac and the valence is saturated with $-CH_2-COOH$, as mentioned in EP 54,812 herein incorporated by reference. Equivalent products are described in said patent.

The residue (XXXVI) is prepared according to UK 2,035,311 herein incorporated by reference, starting from zaltoprofen and having the $-CH(CH_3)-COOH$ end group. Equivalent products are described in said patent.

The preparation process of the residue (XXXVII) is obtained starting from mofezolac and is prepared according to EP 26,928. Equivalents products are reported in the same patent.

The compounds in which R is of the group IV) are described in the British patent application 2,283,238, wherein also the preparation methods are indicated; this patent is herein incorporated by reference.

In the group IV) the compounds can also be obtained: for the compounds of formula (II) using USP 3,904,682; the compounds of formula (X) according to USP 4,161,538, the compounds of formula (III) according to USP 3,228,831. These patents herein mentioned are here incorporated by reference.

In the group V) the compounds can also be obtained: for the compounds of formula (II) using USP 4,089,969 herein incorporated by reference; the compounds of formula (V) can be obtained according to USP 4,556,672 herein incorporated by reference.

The residue (X) is prepared according to the German patent 2,756,113. Equivalent products are described in said patent.

The residue (XI) is prepared according to EP 147,177, herein incorporated by reference, starting from ampiroxicam having the $-CH(CH_3)OCOOC_2H_5$ end group. Equivalent products are described in said patent.

The residue (XII) is prepared according to J. Med. Chem., vol. 27 n. 11, Nov. 1984, Walsh et Al. "Antiinflammatory Agents. 3. Synthesis and Pharmacological Evaluation of 2-amino-3-benzoylphenylacetic Acid and Analogues", herein incorporated by reference. Equivalent products are described in said publication.

The residue (XIII) is prepared starting from lornoxicam, wherein the valence is saturated with H. It is prepared according to GB 2,003,877. Equivalent products are described in said patent.

Generally the connection between A and X_1 is, as seen, of ester or amidic type (NH or NR_{1c}, as defined in X) when R is of groups I, II, III, IV and V. All well known synthesis routes for forming such bonds may be used to form said connection.

In the case of esters of groups I, II, III and IV, and for the compounds of group V ending with a carboxylic function, the most direct synthetic route to obtain the corresponding nitroxyderivatives of the present invention

involves:

a) reaction of the acyl chlorides R-CO-Cl with halogen alcohols of the HO-X_{1z}-Cl, HO-X_{1z}-Br, HO-X_{1z}-I type, wherein X_{1z} is X_1 as above defined without the oxygen atom, in the experimental conditions of the prior art, and isolation of compounds of formula R-CO-O-X_{1z}-Cl(Br,I). The above products can also be obtained by reaction of the sodium or potassium salts of said R-CO-OH acids with dihalogen derivatives of general formula $X_{1z}Cl_2$, $X_{1z}Br_2$ or $X_{1z}I_2$.

b) The above products are transformed into the final products by reaction with $AgNO_3$ in acetonitrile, according to what known in the prior art.

The general schemes are the following:

R-CO-Cl+HO-X_{1z}-Br -----→ R-CO-O-X_{1z}-Br + $AgNO_3$ -----→ A-X_1NO_2

wherein X_1 = $X_{1z}O$.

R-CO-ONa + Br_2X_{1z} -----→ R-CO-O-X_{1z}-Br + $AgNO_3$ -----→ A-X_1NO_2

wherein X_1 = $X_{1z}O$.

In the case of amides the synthetic sequence involves the reaction of the same acyl chlorides RCOCl with aminoalcohols of general formula NH_2-X_{1z}-OH, NHR_{1c}-X_{1z}-OH to give amides of general formula:

R-CO-NH-X_{1z}-OH and R-CO-NR_{1c}-X_{1z}-OH

according to known methods.

The reaction of said amides with halogenating agents such

as for example PCl_5, PBr_3, $SOCl_2$ etc. leads to halogen derivatives of general formula:

$R\text{-}CO\text{-}NH\text{-}X_{1z}\text{-}Br(Cl)$ and $R\text{-}CO\text{-}NR_{1c}\text{-}X_{1z}\text{-}Br(Cl)$.

The latter by reaction with $AgNO_3$ in acetonitrile, according to known methods in the prior art, lead to the final products $A\text{-}X_1\text{-}NO_2$.

The synthesis scheme is the following:

$$R\text{-}CO\text{-}Cl + NHR_{1c}\text{-}X_{1z}\text{-}OH \dashrightarrow R\text{-}CO\text{-}NR_{1c}\text{-}X_{1z}\text{-}OH \xrightarrow{PCl_5} \dashrightarrow$$

$$R\text{-}CO\text{-}NR_{1c}\text{-}X_{1z}\text{-}Cl + AgNO_3 \dashrightarrow R\text{-}CO\text{-}NR_{1c}\text{-}X_{1z}\text{-}ONO_2$$

wherein $X_{1z}O$ is X_1.

c) An alternative route to the synthesis through steps a) and b) above is the reaction of the acid sodium or potassium salts with the nitric esters of halogeno-alcohols of general formula:

$$NO_2\text{-}O\text{-}X_{1z}\text{-}Cl(Br,I)$$

to give directly the nitroxy derivatives of the invention.

The reaction scheme is the following:

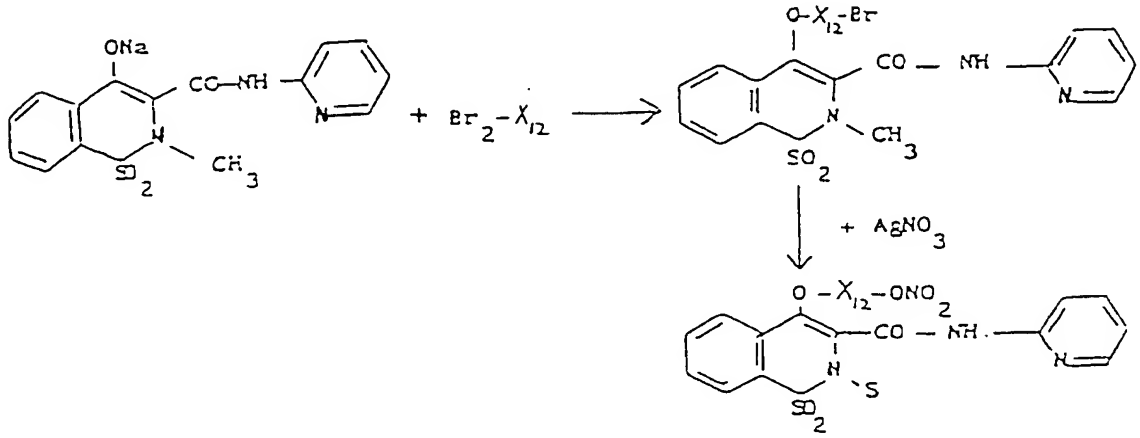
$$R\text{-}CO\text{-}ONa + Br\text{-}X_{1z}\text{-}ONO_2 \dashrightarrow R\text{-}CO\text{-}O\text{-}X_{1z}\text{-}ONO_2$$

wherein $X_{1z}O$ is X_1.

Synthetic routes similar to those above described are used for the products of group V, for example tenoxicam and piroxicam, wherein a dihalogen derivative of formula Br_2X_{1z} is reacted with the corresponding enolates. The products obtained

are then transformed into the compounds of the invention by reaction with $AgNO_3$ in acetonitrile according to the above reported reaction scheme.

The scheme is herein reported for the piroxicam of formula IX of group V.



Group V products, such as tenoxicam and piroxicam, wherein the antiinflammatory reactive function is an hydroxyl, can be also reacted with an acyl chloride of formula $ClCO\text{-}X_{1z}\text{-}Q_I$ wherein Q_I is Cl, Br, I, OH. When Q_I = OH, the hydroxyl is substituted with an halogen as above described before the final nitration reaction with $AgNO_3$.

Nitration is carried out as above described.

In order to obtain the compounds of formula $A\text{-}X_1\text{-}NO$, acyl chlorides of formula R-COCl are reacted with $HX\text{-}X_{1z}\text{-}OH$, wherein R, X and X_{1z} have the above mentioned meanings, in the experimental conditions described in the prior art. The obtained alcohols are reacted with sodium nitrite in a

solvent, for instance constituted of a mixture of water with tetrahydrofuran in the presence of hydrochloric acid. The reaction is described in the prior art. The general scheme is the following:

$R\text{-}COCl + HX\text{-}X_{1z}\text{-}OH \dashrightarrow R\text{-}CO\text{-}X\text{-}X_{1z}\text{-}OH + NaNO_2 \dashrightarrow A\text{-}X_1\text{-}NO$

The compounds according to the present invention are transformed into the corresponding salts by reaction in organic solvent such as for example acetonitrile and tetrahydrofuran with an equimolecular amount of the corresponding organic or inorganic acid.

Examples of suitable organic acids are: oxalic, tartaric, maleic, succinic, citric acid.

Examples of suitable inorganic acids are: nitric, hydrochloric, sulphuric, phosphoric acid.

Another object of the invention is that it has surprisingly been found that the invention products containing $ON\text{-}(O)_z$ groups are able to exert also an inhibiting effect of the inflammation induced by liposaccharide (LPS) and therefore are usable in septic shock.

This is surprising, since it is well known that generally antiinflammatories do not meaningfully change the nitrosynthetase activity induced by lipopolysaccharides in the rat and therefore they cannot be used in septic shock.

The compounds of the present invention can be used as antiinflammatory drugs or for the therapy and prophylaxis of

cardiovascular diseases and of those pathologies wherein cellular hyperproliferation plays an important pathogenetic role.

It must be understood that when the compounds of the various groups contain at least one asymmetric carbon, the products can be used in racemic form or as single isomers. It is indeed well known that in the therapeutic uses of the invention generally an isomeric form is more active than the others. When the compounds present cis/trans isomers, they can be used in this separated form or in admixture.

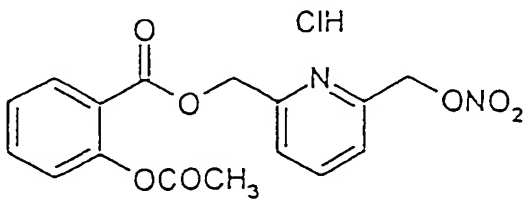
The pharmaceutical formulations of the compounds according to the present invention contain the same dose of the antiinflammatory precursor products, or lower.

The pharmaceutical formulations can be given by os or parenterally and can be prepared according to well known processes in the prior art. See the volume "Remington's Pharmaceutical Sciences".

The following Examples are given for illustrative purposes but are not limitative of the present invention.

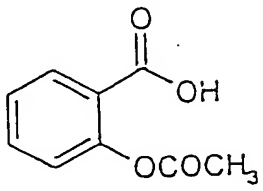
EXAMPLE 1

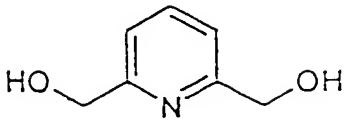
Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester chlorhydrate (NCX 4050) of formula:



(NCX 4050)

starting from the acetylsalicylic acid (formula F1A) and 2,6-bis-(hydroxymethyl)pyridine (formula F1B)





(F1A) (F1B)

A) -Synthesis of 2,6-bis-(chloromethyl)pyridine

To thionyl chloride (11.6 ml, 158 mmoles), cooled at 0°C, 2,6-bis-(hydroxymethyl)pyridine (4 g, 28 mmoles) is very slowly added. The obtained solution is left under stirring for 2 hours at room temperature, then the thionyl chloride in excess is evaporated at reduced pressure. The obtained residue is treated with chloroform and evaporated again at reduced pressure to eliminate the thionyl chloride residues. The crude product is treated with chloroform and washed with water. The organic phase is anhydrified with sodium sulphate and dried obtaining 4.81 g of the product as white solid having m.p. = 76°-78°C.

B) -Synthesis of 2-acetylbenzoic acid 6-(chloromethyl)-2-methylpyridinyl ester

To a solution of salicylic acid (1.6g, 8.88 mmoles) in N,N'-dimethylformamide (20 ml) and under stirring sodium ethylate (0.64 g, 8.88 mmoles) is added. After 30 minutes the

obtained solution is added to a solution of 2,6-bis-(chloromethyl)pyridine (4.72 g, 26.81 mmoles) in N,N'-dimethylformamide (20 ml). The solution is left at room temperature for 7 days, under stirring, then is diluted with ethyl ether and washed with water. The separated organic phases are anhydrified with sodium sulphate and the solvent is evaporated at reduced pressure. The reaction crude product is purified by chromatography on silica gel by eluting with n-hexane/ethyl acetate 7/3. 1.7 g of the product as yellow oil are obtained.
^{1}H-NMR (200MHz)($CDCl_3$): 8.10(1H,d); 7.74(1H,t); 7.57(1H,t); 7.42(1H,d); 7.33(2H,m); 7.11(1H,d); 5.42(2H,s); 4.67(2H,s); 2.41(3H,s).

C) -Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methylpyridinyl ester

To a solution of 2-acetylbenzoic acid 6-(chloromethyl)-2-methylpyridinyl ester (1.5 g, 4.7 mmoles) in acetonitrile (20 ml) maintained under stirring, silver nitrate is added (1.3 g, 7.65 mmoles). The solution is heated to 80°C, maintaining it sheltered from light, under stirring for 30 hours. The formed silver chloride is filtered, the solvent is evaporated. The reaction crude product is purified by silica gel chromatography by eluting with n-hexane/ethyl acetate 7/3. 1.2 g of product as yellow oil are obtained.
^{1}H-NMR (200MHz)($CDCl_3$): 8.10(1H,d); 7.74(1H,t); 7.57(1H,t); 7.42(1H,d); 7.33(2H,m); 7.11(1H,d); 5.60(2H,s); 5.42(2H,s);

2.41(3H,s).

D) -Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2- methylpyridinyl ester hydrochloride

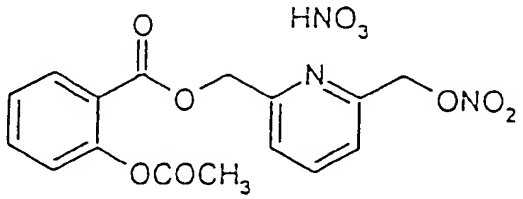
To a solution of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methylpyridinyl ester (1 g, 2.88 mmoles) in ethyl acetate (20 ml) cooled at 0°C, a solution of ethyl acetate/HCl 5M is added by dropping under stirring. It is left for one hour at 0°C, then the temperature is let reach room values. The formed precipitate is filtered and washed with ethyl ether. 900 mg of solid product are obtained.

Elementary analysis

Calculated	C 50.21%	H 3.95%	N 7.31%	Cl 9.26%
Found	C 50.23%	H 3.97%	N 7.29%	Cl 9.20%

EXAMPLE 2

Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester nitrate (NCX 4051) of formula:



(NCX 4051)

starting from the 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methylpyridinyl ester, isolated at step C) of the previous Example 1.

Synthesis of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methyl-

pyridinyl ester nitrate

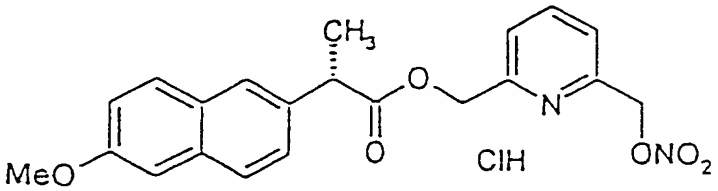
To a solution of 2-acetylbenzoic acid 6-(nitroxymethyl)-2-methylpyridinyl ester (1 g, 2.88 mmoles) in acetonitrile (10 ml) cooled at 0°C, a solution of 65% nitric acid (0.2 ml) in acetonitrile (2 ml) is added by dropping under stirring. It is left for 2 hours at 0°C, then the temperature is let reach room values. The formed precipitate is filtered and washed with ethyl ether. 1 g of solid product is obtained.

Elementary analysis

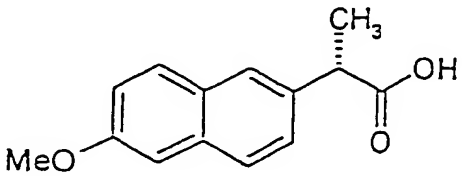
Calculated	C 46.95%	H 3.69%	N 10.26%
Found	C 46.99%	H 3.72%	N 10.22%

EXAMPLE 3

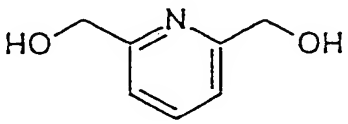
Synthesis of the (S)-6-methoxy-α-methylnaphthaleneacetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride of formula:



starting from naproxen (formula F3A) and 2,6-bis-(hydroxymethyl)pyridine (formula F1B)



(F3A)



(F1B)

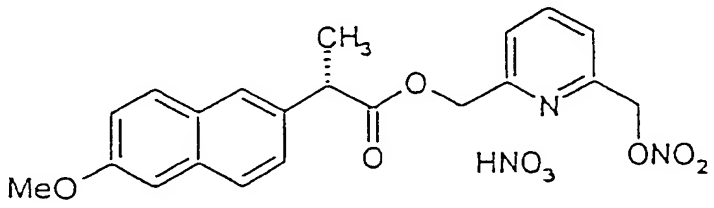
The compound is synthetized following the procedure repeorted in Example 1. Yield 38%.

Elementary analysis

Calculated	C 58.25%	H 4.88%	N 6.47%	Cl 8.19%
Found	C 58.29%	H 5.00%	N 6.44%	Cl 8.11%

EXAMPLE 4

Synthesis of the (S)-6-methoxy-α-methylnaphthaleneacetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester nitrate of formula:



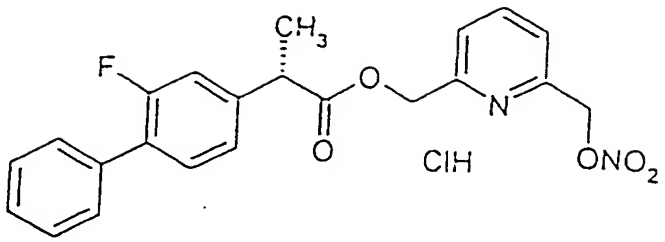
The compound is synthetized following the procedure reported in Example 2. Yield 42%.

Elementary analysis

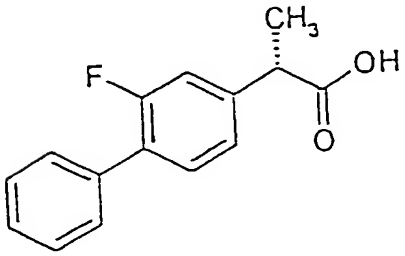
Calculated	C 54.88%	H 4.60%	N 9.15%
Found	C 54.91%	H 4.65%	N 9.10%

EXAMPLE 5

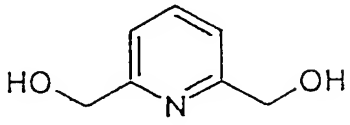
Synthesis of the 2-fluoro-α-methyl-(1,1'biphenyl)-4-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride of formula:



starting from flurbiprofen (Formula F5A) and 2,6-bis-(hydroxymethyl)pyridine (formula F1B)



(F5A)



(F1B)

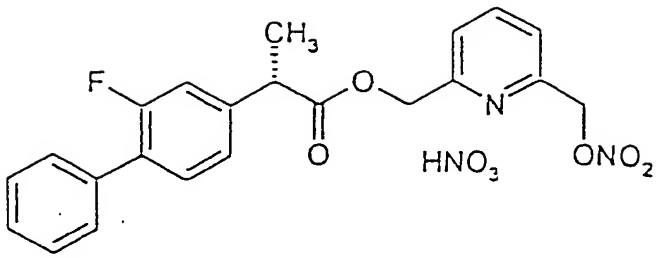
The compound is synthetized following the procedure reported in Example 1. Yield 35%.

Elementary analysis

Calculated	C 59.12%	H 4.51%	N 6.29%	Cl 7.93%	F 4.25%
Found	C 59.17%	H 4.55%	N 6.21%	Cl 7.91%	F 4.22%

EXAMPLE 6

Synthesis of the 2-fluoro-α-methyl-(1,1'biphenyl)-4-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester nitrate of formula:



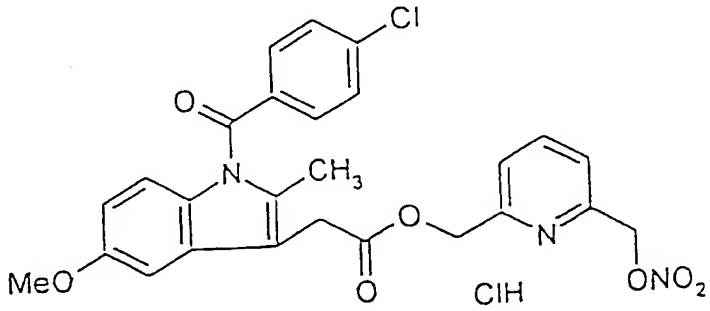
The compound is synthetized following the procedure reported in Example 2. Yield 39%.

Elementary analysis

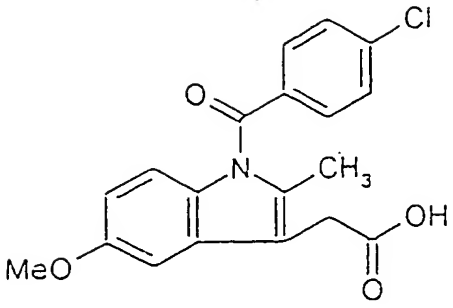
Calculated	C 55.79%	H 4.26%	N 8.91%	F 4.01%
Found	C 55.83%	H 4.30%	N 8.88%	F 4.00%

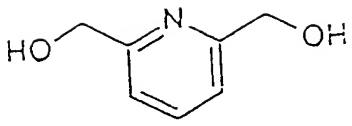
EXAMPLE 7

Synthesis of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride of formula:



starting from indomethacin (Formula F7A) and 2,6- bis-(hydroxymethyl)pyridine (formula F1B)





(F7A) (F1B)

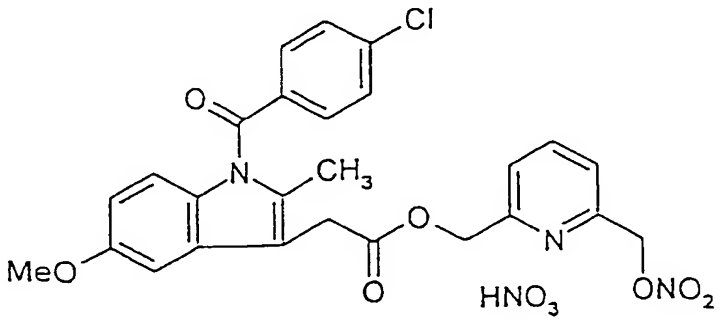
The compound is synthetized following the procedure reported in Example 1. Yield 41%.

Elementary analysis

Calculated	C 55.71%	H 4.13%	N 7.53%	Cl 12.65%
Found	C 55.73%	H 4.16%	N 7.49%	Cl 12.64%s

EXAMPLE 8

Synthesis of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester nitrate of formula:



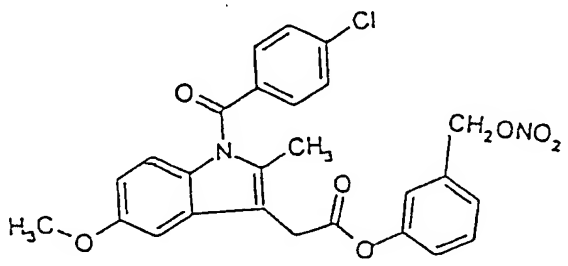
The compound is synthetized following the procedure reported in Example 2. Yield 35%.

Elementary analysis

Calculated	C 53.18%	H 3.95%	N 9.58%	Cl 6.04%
Found	C 53.20%	H 4.41%	N 9.56%	Cl 6.01%

EXAMPLE 9 (comparative)

Preparation of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(nitroxymethyl)phenyl ester of formula:



wherein the precursor drug is indomethacin (formula F7A).

a) -Synthesis of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(formyl)phenyl ester

To a solution of 3-hydroxybenzaldehyde (g 8.30) and triethylamine (g 0.824) in methylene chloride (200 ml), cooling at a temperature in the range -5°C-0°C indomethacin in the form of the corresponding acylchloride (g 16.50) is added under stirring. It is still maintained under stirring for 15 minutes, then water (100 ml) is added and the phases are separated. The aqueous phase is recovered and extracted with methylene chloride (300 ml). The organic phases are joined together, washed with a 5% Na_2CO_3 solution, the organic phase is anhydrified with sodium sulphate obtaining the expected

compound.

b) -Synthesis of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(hydroxymethyl)phenyl ester

The compound isolated in the previous step (g 1.9) is dissolved in ethyl acetate (100 ml) in the presence of palladium 5% on carbon (g 0.290) with the 50% of humidity. The mixture is hydrogenated at room temperature and hydrogen pressure of about 2.5 atm, under stirring. After 12 hours the catalyst is removed by filtration under vacuun, washing with ethyl acetate (200 ml). The organic phases are joined together and washed with a 5% sodium bicarbonate solution and water. It is anhydrified with magnesium sulphate. It is filtered under vacuum and evaporated at reduced pressure obtaining the expected compound.

c) -Synthesis of 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(chloromethyl) phenyl ester

To a mixture formed by the compound isolated in the previous step (g 1.85) and thionyl chloride (ml 5.5), maintained under stirring, dimethylformamide (ml 0.5) is added at room temperature and left under stirring for one hour. At the end the thionyl chloride is evaporated at reduced pressure at a bath temperature lower than 40°C. The so obtained crude solid product is purified by crystallization with isopropyl ether (ml 30).

A solid is isolated which is dried under vacuum at room

temperature, obtaining the expected compound.

d) -Synthesis of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(nitroxymethyl) phenyl ester

A solution of the compound isolated in the previous step (1.4 g) in acetonitrile (ml 8) is treated under stirring, sheltered from light and at room temperature with $AgNO_3$ (g 0.9). It is heated at reflux for two hours and then cooled at room temperature and $AgNO_3$ (g 1.2) is added. It is filtered under vacuum, the precipitate (silver salts) is washed with acetonitrile. The organic phase is evaporated under vacuum at a bath temperature lower than 40°C. The obtained crude product is crystallized from isopropyl ether.

The process global yield is 34%. By analyzing the final product by chromatography on thin layer of silica gel, using as eluent hexane/ethyl acetate 7/3, an unitary stain is obtained. m.p. 115-117°C. ^{1}H-NMR ($CDCl_3$): 7.70 (2H, d), 7.49 (2H, d), 7.42 (1H, t), 7.14-7.06 (4H, m), 6.90 (1H, d), 6.70 (1H, dd), 5.42 (2H, s), 3.93 (2H, s), 3.86 (3H, s) 2.48 (3H, s).

EXAMPLE 10 (comparative)

Synthesis of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 4-nitroxybutyl ester

To a solution of indomethacin (5.04 g, 14 mmoles) in chloroform (50 ml) at room temperature 1-chloro-4-butanol (1.4 ml, 14 mmoles), N,N' dicyclohexylcarbodiimide (2.87 g, 14 mmoles) and 4-dimethylaminopyridine (0.11 g, 0.09 mmoles) are

added. The mixture is maintained under stirring at room temperature for 6 hours. The solid is filtered and the organic phase is washed with water, separated, dried with sodium sulphate and finally evaporated under vacuum. The obtained residue is purified by column chromatography (eluent n-hexane/ethyl acetate 9/1). An yellow-coloured oily residue (5.2 g), corresponding to 4-chlorobutyl ester of the indomethacin is isolated.

5 g of the compound (11 mmoles) are dissolved in acetonitrile (25 ml) and treated with silver nitrate (3.8 g, 22 mmoles). The mixture is let reflux in the dark for 48 hours. After cooling, the solid residue is filtered and the solvent is evaporated under vacuum. The obtained residue is purified by column chromatography (eluent n-hexane/ethyl acetate 9/1). At the end an oil (4.2 g) is isolated.

^{1}H-NMR ($CDCl_3$, ppm): 7.65 (2H, m); 7.45 (2H, m); 6.95 (1H, d); 6.84 (1H, d); 6.66 (1H, dd); 4.10 (2H, t); 3.82 (3H, s); 3.65 (2H, s); 3.35 (2H, t); 2.39 (3H, s); 1.80 (4H, m).

EXAMPLE 11

Solubility tests

Solubility tests in water of the salts of the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester (Ex. 7 and 8) by comparison with the 1-(4-chorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 3-(nitroxymethyl)phenyl ester (Ex. 9) and

with the 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-acetic acid 4-nitroxybutyl ester have been carried out.

Said solubility tests have been effected by adding, at room temperature, in a 50 ml flask, 5 g of the substance and then bringing to volume with water.

The compounds according to the invention completely dissolve, therefore they show a solubility equal to at least 100 mg/ml.

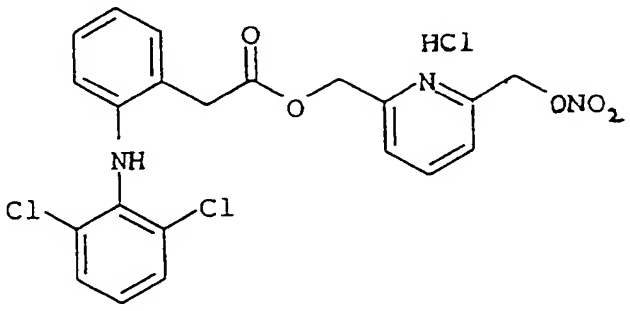
The comparative compounds under the same conditions are unsoluble.

EXAMPLE 12

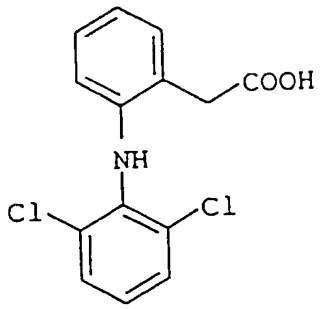
Example 11 has been repeated with the compounds from 1 to 6. All the compounds result soluble in water under the same conditions of the previous Example.

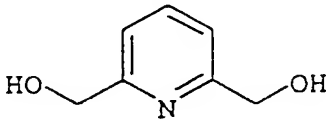
EXAMPLE 13

Synthesis of 2-[(2,6-dichlorophenyl)aminobenzeneacetic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride of formula:



starting from 2-[(2,6-dichlorophenyl)aminobenzeneacetic acid sodium salt (formula) and 2,6-bis-(hydroxymethyl)pyridine





(F9A) (F1B)

A) -Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(chloromethyl)-2-methylpyridinil ester

To a solution of 2,6-bis-(chloromethyl)pyridine (3.83 g, 21.75 mmoles), prepared as described in Example 1 A, in N,N'-dimethyl formamide (20 ml), under stirring, a solution of 2-[(2,6-dichloro phenyl)amino]benzene acetic acid sodium salt (3.04 g, 9.54 mmoles) in N,N'-dimethylformamide (25 ml) is added dropwise. The solution is stirred at room temperature for one day, then it is diluted with ethyl acetate and washed with water. The organic phases are recovered and anhydrified with sodium sulphate. The solvent is then evaporated under a reduced pressure. The crude reaction product is purified by chromatography on a silica gel column, eluted with n-hexane/

ethyl acetate 8/2. 2.88 g of the product are obtained as a white solid. Yield 69%

^{1}H NMR (200MHz) ($CDCl_3$): 7.66 (1H, t); 7.41 (1H, d); 7.33 (1H, d); 7.27 (1H, d); 7.18 (2H, m); 6.97 (2H, dd); 6.81 (1H, s); 6.57 (1H, d); 5.3 (2H, s); 4.62 (2H, s); 3.93 (2H, s).

B) -Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methyl pyridinyl ester

To a stirred solution of 2-[(2,6-dichlorophenyl)amino-benzene acetic acid 6-(chloromethyl)-2-methylpyridinil ester (2.438 g, 5.59 mmoles) in 90 ml of acetonitrile is added silver nitrate (2.19 g, 12.89 mmoles). The solution is further stirred for 30 hours at 80°C maintaining it sheltered from light. The formed silver chloride is filtered and the solvent evaporated. The crude reaction product is purified by silica gel column chromatography, eluted with n-hexane/ethyl acetate 7/3. 1.2 g of the product in the form of a yellow oil are obtained. Yield 46%.

^{1}H NMR (200MHz) ($CDCl_3$): 7.69 (1H, dd); 7.33 (1H, d); 7.25 (1H, m); 7.23 (2H, m); 7.16 (1H, dd); 6.98 (2H, m); 6.82 (1H, s); 6.57 (1H, d); 5.49 (2H, s); 5.31 (2H, s); 3.94 (2H, s).

C) -Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methyl pyridinyl ester hydrochloride

To a solution of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methylpyridinil ester (0.400 g, 0.86 mmoles) in ethyl acetate (6 ml), cooled at 0 °C, a

solution of HCl/ ethyl acetate 3M (0.6 ml) is added dropwise under stirring. the reaction mixture is stirred for one hour at 0 °C, then is warmed up to room temperature.

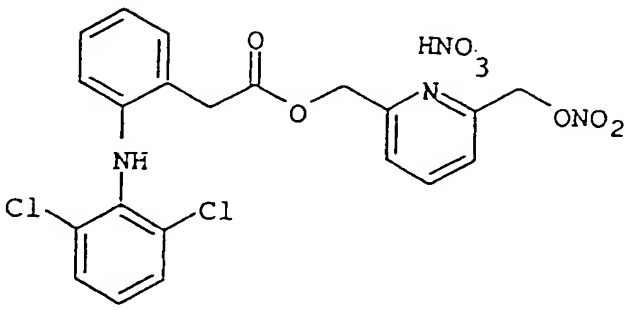
The formed precipitate is filtered and washed with ethyl ether. 0,310 g of solid product are obtained. Yield 73%.

Elementary analysis

Calculated:	C 50.58%	H 3.63%	N 8.42%	Cl 21.32%
Found:	C 50.62%	H 3.66%	N 8.40%	Cl 21.02%

EXAMPLE 14

Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methyl pyridinyl ester nitrate of formula:



starting from 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methylpyridinil ester, obtained in step B) of the previous example 13.

Synthesis of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methyl pyridinyl ester nitrate

To a solution of 2-[(2,6-dichlorophenyl)aminobenzene acetic acid 6-(nitroxymethyl)-2-methylpyridinil ester (0.760 g, 1.65 mmoles) in acetonitrile (6 ml), cooled at 0 °C, a solution of nitric acid (65%) (0.150 ml) in acetonitrile (2 ml) is added dropwise, under stirring. The reaction mixture is stirred one hour at 0 °C, then is warmed up to room temperature. The formed precipitate is filtered and washed with ethyl ether. 0,600 g of the product, in the form of a solid, are obtained. Yield 70%.

Elementary analysis

Calculated:	C 48.02%	H 3.45%	N 10.67%	Cl 13.50%
Found:	C 48.06%	H 3.47%	N 10.66%	Cl 13.60%

EXAMPLE 15

Study of the inhibition effect on smooth muscle contraction and smooth muscle cell proliferation

As known, contraction and/or cell proliferation of smooth muscle are important steps in the inflammation process.

Smooth muscle contraction

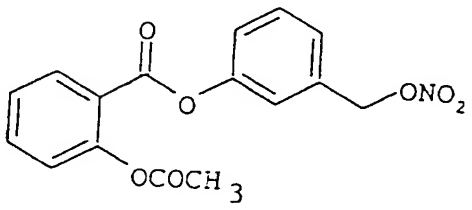
New Zealand White Rabbits (2.0-2.5 kg) were killed by cervical dislocation, cavernosal tissue (corpus cavernosus) and aorta excised.

The tissue was mounted in organ baths for recording of isometric tension, according to the method described by Khan MA et al (BJU Int. 1999 84(6):720-4). Tissues were pre-contracted with phenylephrine (10 μM) and relaxation responses

to carbachol assessed in the presence of the compound to be tested.

The compound of the invention used in the assay was 2-acetylbenzoic acid 6-(nitroxymethyl)-2-pyridinylmethyl ester hydrochloride (NCX 4050), which synthesis is described in preceding example 1.

The reference compound was 2-acetoxybenzoic acid (3-nitroxymethyl)phenyl ester of formula



(NCX 4016)

which synthesis is described in ex. 3 of the PCT patent application WO 97/16405 filed in the Applicant's name.

Results are given in following Table 1, that showsthat the compound of the invention is more active than the reference compound in inhibiting smooth muscle contraction.

Smooth muscle cell proliferation

Human saphenous veins were cultured by standard explant methods (J. Cardiovasc. Pharmacol. 1999, 33(2), 204-11). Tissues were collected into sterile pots containing PBS, penicillin and streptomycin. Under sterile tissue culture conditions, tissues were cut into small pieces (approximately

1 mg weight) and placed into a standard culture medium containing 20 % fetal calf serum (FCS) for several days (medium changed every 2-4 days). ^{3}H-thymidine was measured in the DNA fraction of cells cultured into 48 well plates. Cells were cultured to confluence in the medium containing 10% FCS. Cells were deprived of serum for 24 h before the addition of 10% FCS, together with different concentration of steroids. After 24 h, ^{3}H-thymidine was added to the cells for 4 h. Cells were washed with phosphate buffered saline and ethanol. DNA was extracted with sodium hydroxide solution and the ^{3}H material counted by scintillation. The data represents observations made in triplicate wells.

Table 2 reports results obtained on the inhibitory effect of the tested compounds on human vascular smooth cell proliferation.

The Table shows that the compound of the invention is much more active than the reference compounds.

Table 1 and 2 demonstrate that the antiinflammatory activity of the compound of the invention is higher than that of the reference compound.

Table 1

Inhibition of aorta and corpus cavernosum smooth muscle contraction at different concentrations (10^{-4} and 10^{-5} M) of the compound of the invention (NCX 4050) and of the reference compound (NCX 4016)			
sample	concentration (log M)	% inhibition rabbit aorta	% inhibition rabbit corpus cav.
NCX 4050	- 4	87	85
	- 5	80	63
NCX 4016 (comp.)	- 4	20	47
	- 5	18	14

Table 2

Inhibition of smooth muscle cell proliferation at different concentrations (10^{-4} and 10^{-5} M) of the compound of the invention (NCX 4050) and of the reference compound (NCX 4016)		
sample	concentration (log M)	% inhibition cell proliferation
NCX 4050	- 4	95
	- 5	82
NCX 4016 (comp.)	- 4	60
	- 5	43

CLAIMS

1. Organic or inorganic salts of compounds of general formula:

$$A - X_1 - N(O)_z$$

wherein:

z is an integer and is 1 or 2;

A = $R(COX_u)_t$ and wherein t is an integer 0 or 1; u is 0 or 1;

X = O, NH, NR_{1c} wherein R_{1c} is a linear or branched C_1-C_{10} alkyl.

$$X_1 = -[C]_{nIX}(R_{TIX})(R_{TIX'})- Y -[C]_{nIIX}(R_{TIIX})(R_{TIIX'})-O- \qquad (B)$$

wherein:

nIX is an integer between 0 and 3;

nIIX is an integer between 1 and 3;

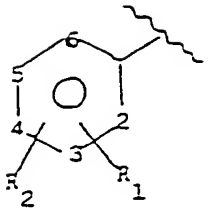
R_{TIX}, $R_{TIX'}$, R_{TIIX}, $R_{TIIX'}$, equal to or different from each other, are H or a linear or branched C_1-C_4 alkyl;

Y is a ring containing at least one salifiable nitrogen atom; preferably Y is an heterocyclic ring, saturated or unsaturated or aromatic, having preferably 5 or 6 atoms and containing at least one or two nitrogen atoms;

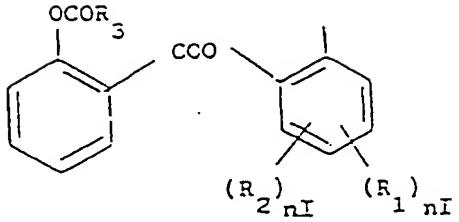
R is selected from the following groups:

Group I) wherein t = 1 and u = 1

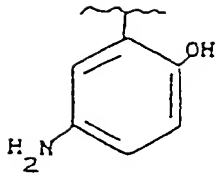
Ia)



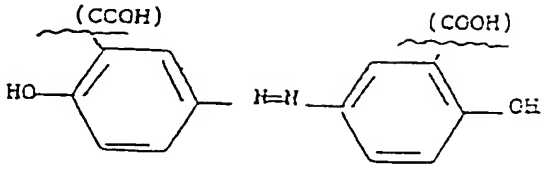
Ib)



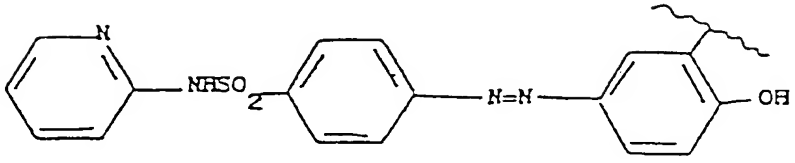
Ic)



IC_1)



IC_2)



IC_3)

wherein:

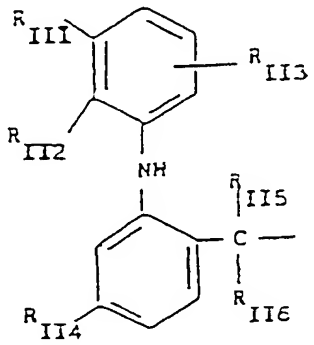
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3-C_5 alkyl, or the residue of a heterocycle with a single ring having 5 or 6 atoms which may be aromatic, partially or totally hydrogenated, containing one or more hetero-atoms independently selected from O, N and S;

R_2 is hydrogen, hydroxy, halogen, a linear or when possible branched C_1-C_4 alkyl, a linear or when possible branched C_1-C_4 alkoxyl; a linear or when possible branched C_1-C_4 perfluoroalkyl, for example trifluoromethyl; nitro, amino, mono- or di-(C_{1-4}) alkylamino;

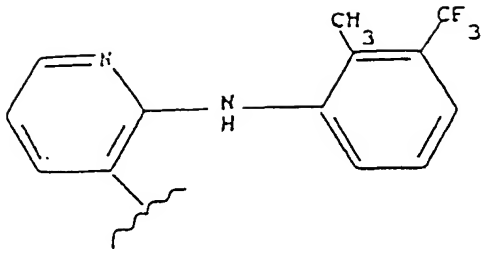
nI is an integer 0 or 1;

Group II) wherein t = 1, u = 1

IIa)



IIb)



wherein:

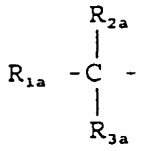
R_{II5} is H, a linear or when possible branched C_1-C_3 alkyl;

R_{II6} has the same meaning as R_{II5}, or when R_{II5} is H it may be benzyl;

R_{III}, R_{II2} and R_{III3} can independently be hydrogen, a linear or when possible branched C_1-C_6 alkyl or a linear or when possible branched C_1-C_6 alkoxy, or Cl, F, Br;

R_{II4} is R_{III} or bromine;

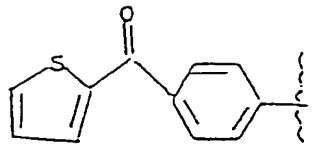
Group III) wherein t = 1, u = 1 and R is



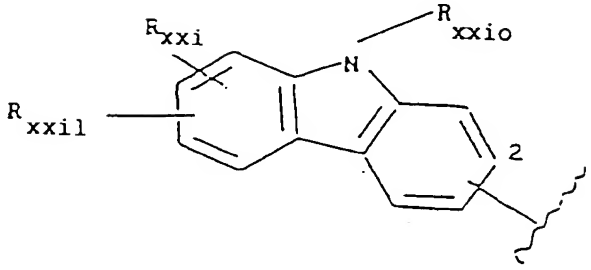
wherein:

R_{2a} and R_{3a} are H, a linear or when possible branched, substituted or non-substituted, C_1-C_{12} alkyl or allyl, with the proviso that when one of the two is allyl, the other is H; preferably R_{2a} is H, C_1-C_4 alkyl, R_{3a} is H;

R_{1a} is selected from



(II)



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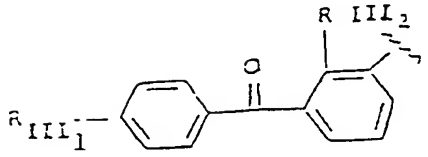

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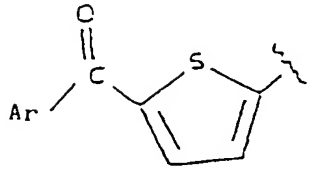

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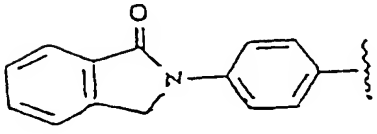

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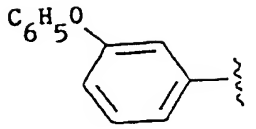

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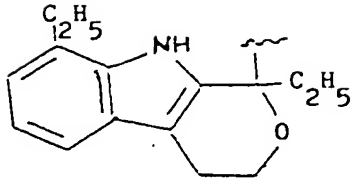
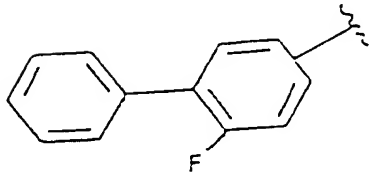


(VIII)



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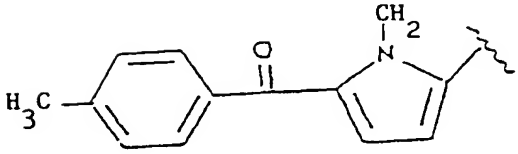
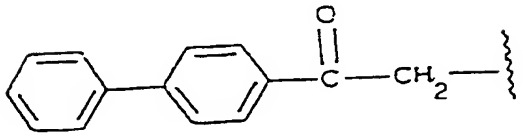
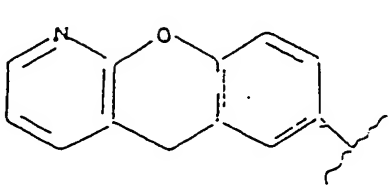


(X)

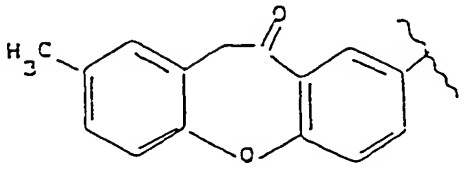


(III)

IIID) R_{1a} corresponds to the following formulas:



IIIa)



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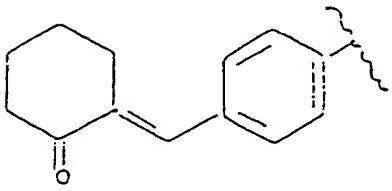
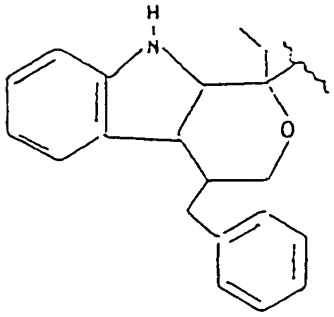


(XXXI)



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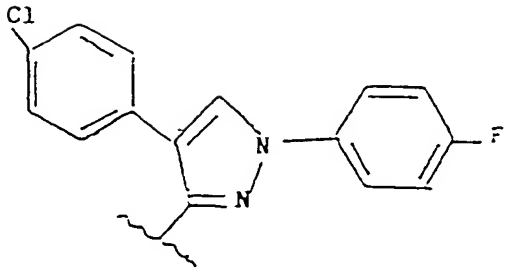

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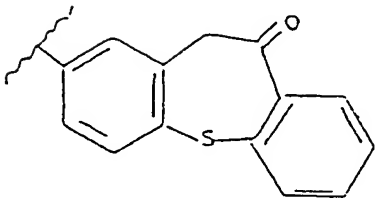

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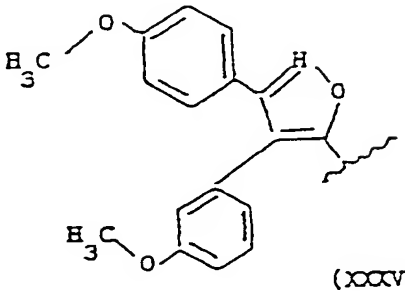
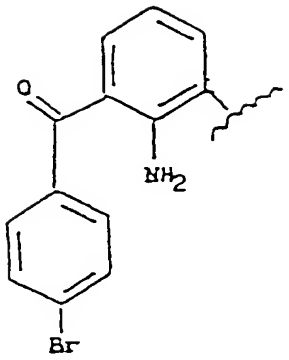


(XXXVII)



(XXII)

wherein the meanings are the following:

- when R_{1a} is as defined in formula (IV), Ketoprofen residue: R_{III1} is H, SR_{III3} wherein R_{III3} contains from 1 to 4 C atoms, linear or branched when possible; R_{III2} is H, hydroxy;
- when R_{1a} is as defined in formula (XXI), carprofen residue: R_{xxio} is H, a linear or when possible branched alkyl from 1 to 6 C atoms, a C_1-C_6 alkoxycarbonyl bound to a C_1-C_6 alkyl, C_1-C_6 carboxyalkyl, C_1-C_6 alkanoyl, optionally substituted with halogens, benzyl or halobenzyl, benzoyl or halobenzoyl;

  R_{xxi} is H, halogen, hydroxy, CN, C_1-C_6 alkyl optionally containing OH groups, C_1-C_6 alkoxy, acetyl, benzyloxy, SR_{xxi2} wherein R_{xxi2} is C_1-C_6 alkyl; C_1-C_3 perfluoroalkyl; C_1-C_6 carboxyalkyl optionally containing OH groups, NO_2, amino; sulphamoyl, di-alkyl sulphamoyl with C_1-C_6 alkyl, or di-fluoroalkylsulphonyl with C_1-C_3 alkyl;

R_{xxii} is halogen, CN, C_1-C_6 alkyl containing one or more OH groups, C_1-C_6 alkoxy, acetyl, acetamido, benzyloxy, SR_{III} being as above defined, C_1-C_3 perfluoroalkyl, hydroxy, C_1-C_6 carboxyalkyl, NO_2, amino, mono- or di-alkyl-amino C_1-C_6; sulphamoyl, di-alkyl sulphamoyl C_1-C_6, or di-fluoroalkylsulphamoyl as above defined; or R_{xxi} together with R_{xxii} is a C_1-C_6 alkylene dioxy;

- when R_{1a} is as defined in the formula (XXXV), residue of the tiaprofenic acid:
  Ar is phenyl, hydroxyphenyl optionally mono- or poly-substituted with halogen, C_1-C_6 alkanoyl and alkoxy, C_1-C_6 trialkyl, preferably C_1-C_3, cyclopentyl, cyclohexyl cycloheptyl, heteroaryl, preferably thienyl, furyl optionally containing OH, pyridyl;
- when R_{1a} is as defined in formula (II), suprofen residue, wherein R_{3a} is H, R_{2a} is methyl and X = O;
- when R_{1a} is as defined in formula (VI), R is the residue of indoprofen when R_{2a} = H and R_{3a} = CH_3 and of indobufen when R_{2a} is equal to H and R_{3a} = C_2H_5; X = O;
- when R_{1a} is as defined in formula (VIII), R is the residue of etodolac when R_{2a} = R_{3a} = H and X = O;
- when R_{1a} is as defined in formula (VII), R is the residue of fenoprofen when R_{3a} = H, R_{2a} = CH_3 and

X = O;

- when R_{1a} is as defined in formula (III), R is the residue of fenbufen wherein R_{2a} = R_{3a} = H and X = O;
- when R_{1a} is as defined in formula (IX), R is the residue of flurbiprofen when R_{3a} = H, R_{2a} = CH_3, X = O;
- in the compounds of formula (X) R is the residue of tolmetin when R_{2a} = R_{3a} = H, X = O;

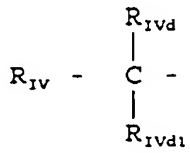
in the group IIID) R_{1a} corresponds to the following formulas:

- IIIa), when R_{2a} = H and R_{3a} = CH_3 the residue of pranoprofen is obtained: α-methyl-5H-[1]benzopyran-[2,3-b]pyridin-7-acetic acid;
- (XXX), when R_{2a} = H and R_{3a} = CH_3 the bermoprofen residue is obtained: dibenz[b,f]oxepin-2-acetic acid;
- (XXXI), when R_{2a} = H and R_{3a} = CH_3, R is the radical of the compound CS-670: 2-[4-(2-oxo-1-cyclohexylidenmethyl) phenyl]propionic acid;
- (XXXII), when R_{2a} = R_{3a} = H the Pemedolac residue is obtained;
- (XXXIII), when R_{2a} = R_{3a} = H the pirazolac residue is obtained: 4-(4-chlorophenyl)-1-(4-fluorophenyl)-3-pyrazolic acid;
- (XXXVI), when R_{2a} = H, R_{3a} = CH_3, the zaltoprofen

residue is obtained; when the residue is saturated with an hydroxyl or aminic group or with the carboxylic function the compounds are known as dibenzothiepin derivatives;

- (XXXVII), when R_{2a} = R_{3a} = H the mofezolac residue is obtained: 3,4-di(p-methoxyphenyl)isoxazol-5-acetic acid;
- (XII), when R_{2a} = R_{3a} = H the bromfenac residue is obtained: 2-amino-3-(4-bromobenzoyl)benzeneacetic acid;

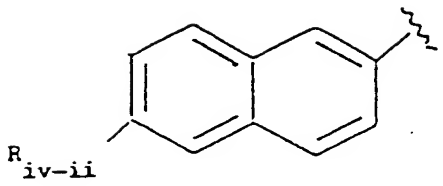
in group IV) wherein t = 1, u = 1, R is



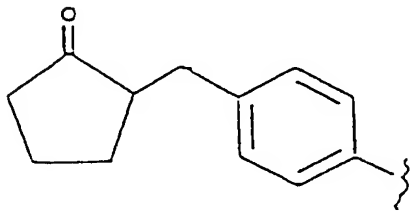
wherein:

R_{IVd} and R_{IVd1} are at least one H and the other a linear or branched when possible alkyl from C_1 to C_6, preferably C_1 and C_2, or difluoroalkyl with the alkyl having from 1 to 6 C atoms, C_1 is preferred, or R_{IVd} and R_{IVd1} form together a methylene group;

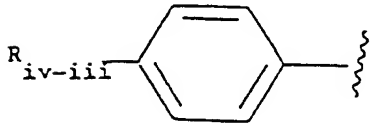
R_{IV} has the following meaning:



(II)



(X)

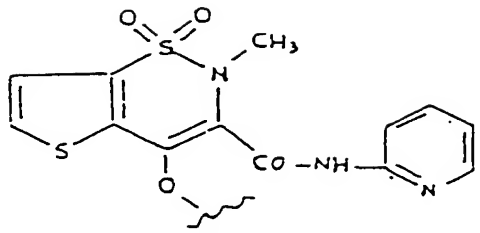


(III)

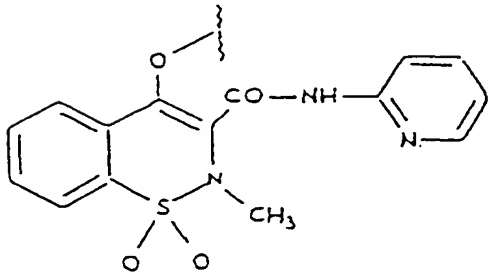
wherein:

- in formula (II) R_{iv-ii} is C_1-C_6 alkyl, C_3-C_7 cycloalkyl, C_1-C_7 alkoxymethyl, C_1-C_3 trifluoroalkyl, vinyl, ethynyl, halogen, C_1-C_6 alkoxy, difluoroalkoxy with the C_1-C_7 alkyl, C_1-C_7 alkoxymethyloxy, alkylthiomethyloxy with the C_1-C_7 alkyl, alkyl methylthio with the C_1-C_7 alkyl, cyano, difluoromethylthio, phenyl- or phenylalkyl substituted with the C_1-C_8 alkyl;
- formula (X), loxoprofen residue;
- in formula (III) R_{iv-iii} is a C_2-C_5 alkyl, optionally branched when possible, C_2 and C_3 alkyloxy, allyloxy, phenoxy, phenylthio, cycloalkyl having from 5 to 7 C atoms, optionally substituted in position 1 with a C_1-C_2 alkyl;

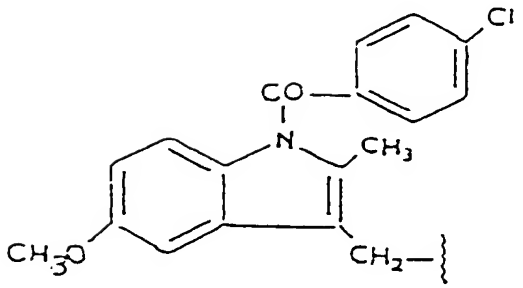
Group V)



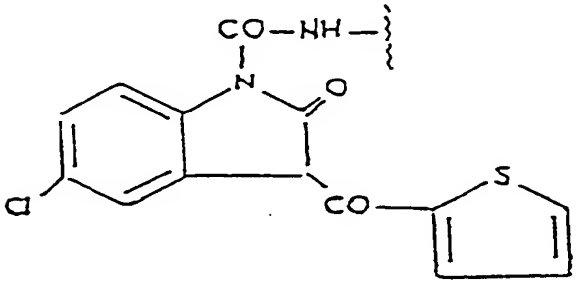
(VII)



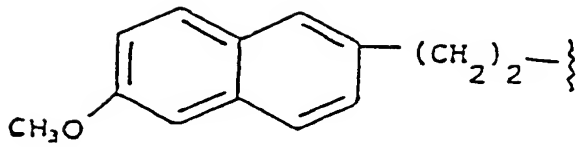
(IX)



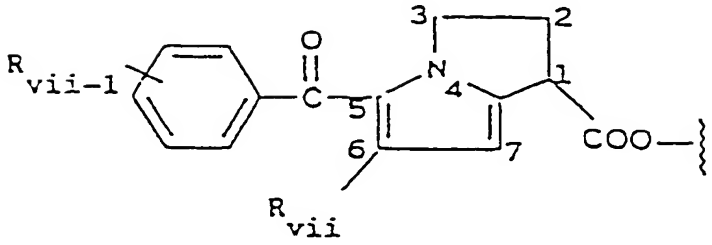
(IV)



(V)

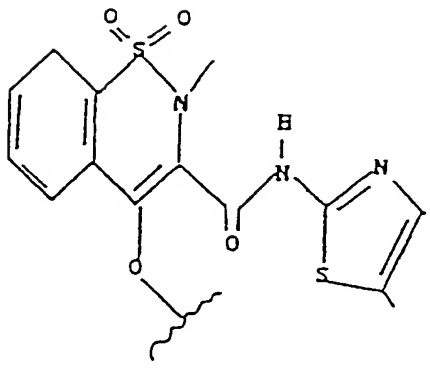


(III)

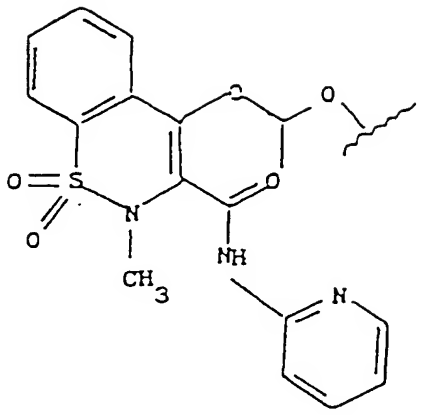


(II)

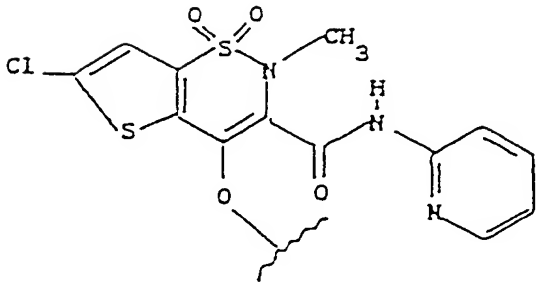
Group VE)



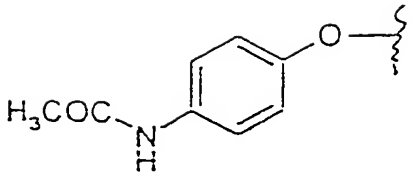
(X)



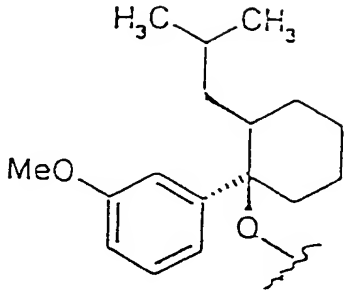
(XI)



(XIII)



(XXIX)



(XXXI)

In group V),

- when R is the formula (II), R_{vii} is H or a linear or branched when possible C_1-C_4 alkyl;
  R_{vii-1} is R_{vii}, or a linear or branched when possible C_1-C_4 alkoxy; Cl, F, Br; the position of R_{vii-1} being ortho, or meta, or para;
- when R is the formula (V), A = R and t = 0;
- when R is the formula (VII), A is RCO, t = 1 u = 0 or A is R and t = 0;
- when R is the formula (IX), A = R and t = 0, or A = RCO with t = 1 and u = 0;
- when R is the formula (III) A = RCOO, t = 1 and u = 0 or 1; or t = 0 and A = R;
- when R is the formula (IV), A = RCOO, t = 1 and u = 1;
- when R is the formula (X), it is the residue of meloxicam;
- when R is constituted of the formula (XI), it is known as ampiroxicam when the end group is $-CH(CH_3)OCOC_2H_5$;
- when R is the formula (XIII) and the free valence is saturated with H, the residue is that of lornoxicam;
- when R is the formula (XXXX) and the valence is saturated with H, the compound is known as paracetamol;

- when R is the formula (XXXXI) and the valence is saturated with H, the residue is known as tramadol.

2. Salts according to claim 1, wherein in the compounds of formula $A\text{-}X_1\text{-}N(O)_z$ z is 2 and nIX and nIIX in the formula (B) of X_1 are integers equal to 1 and R_{IIX}, $R_{IIX'}$, R_{IIIX}, $R_{IIIX'}$ are equal to H.

3. Salts according to claims 1 and 2, wherein in the compounds of formula $A\text{-}X_1\text{-}N(O)_z$ R, X, u and t of the formula $A = R(COX_u)_t$, and Y in formula (B) of X_1, have the following meanings:

when R is selected from Group I),

- in the compounds of formula Ia) X is equal to O or NH, R_1 is acetoxy, preferably in ortho-position with respect to -CO-, R_2 is hydrogen; in X_1 $R_{IIX} = R_{IIX'} = R_{IIIX} = R_{IIIX'} = H$, $n_{IX} = n_{IIX} = 1$ and Y is an aromatic ring having 6 atoms, containing a nitrogen atom, said aromatic ring having the two free valences in position 2 and 6;
- in the compounds of formula Ib) $R_3 = CH_3$, nI = 0, X is equal to O, X_1 is as above defined for Ia); in this case Ib) is the residue of the acetylsalicylsalicylic acid;
- in the compounds of formula 1c) X = O and u = 1;

when R is selected from Group II),

- in the formula IIa R_{II1}, R_{II4} are hydrogen and R_{II2} and

R_{II3} are chlorine in ortho-position with respect to NH; R_{II5} and R_{II6} are H, X is equal to O, and X_1 is as above defined for the compounds of formula Ia);

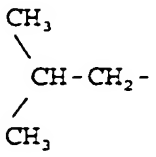
when R is selected from Group III),

- when R_{1a} is as defined in formula (IV), R_{III1} and R_{III2} are H, R_{3a} is H, and R_{2a} is methyl, X = O;
- when R_{1a} is as defined in formula (XXI), R_{xxio} is H, the linking bridge is in position 2, R_{xxi} is H, R_{xxii} is chlorine and is in para position with respect to nitrogen;
- when R_{1a} is as defined in the formula (XXXV), Ar is phenyl, R_{3a} is H, R_{2a} is methyl and X is O; R_{3a} is H, R_{2a} is methyl and X is O;
- when R_{1a} is as defined in the formula IIIa), R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- when R_{1a} is as defined in the formula (XXX) R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- when R_{1a} is as defined in the formula (XXXI), R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;
- when R_{1a} is as defined in the formula (XXXII), R_{2a} = R_{3a} = H, u = 1 and X = O;
- when R_{1a} is as defined in the formula (XXXIII), R_{2a} = R_{3a} = H, u = 1 and X = O;
- when R_{1a} is as defined in the formula (XXXVI), R_{2a} = H, R_{3a} = CH_3, u = 1 and X = O;

- when R_{1a} is as defined in the formula (XXXVII), R_{2a} = R_{3a} = H, t = 1 and X = O;
- when R_{1a} is as defined in the formula (XII), R_{2a} = R_{3a} = H, u = 1, t = 1, X = O, R_{2a} = R_{3a} = H; or t = 0

when R is selected from Group IV),

- when R_{IV} is the formula (II), R_{iv-ii} = CH_3O-, R_{IVd} = H and R_{IVd1} = CH_3, X = O and X_1 is as above defined for Ia);
- when R_{IV} is the formula (X), R_{IVd} = H, R_{IVd1} = CH_3, X = O and X_1 is as above defined for Ia);
- when R_{IV} is the formula (III), R_{iv-iii} is



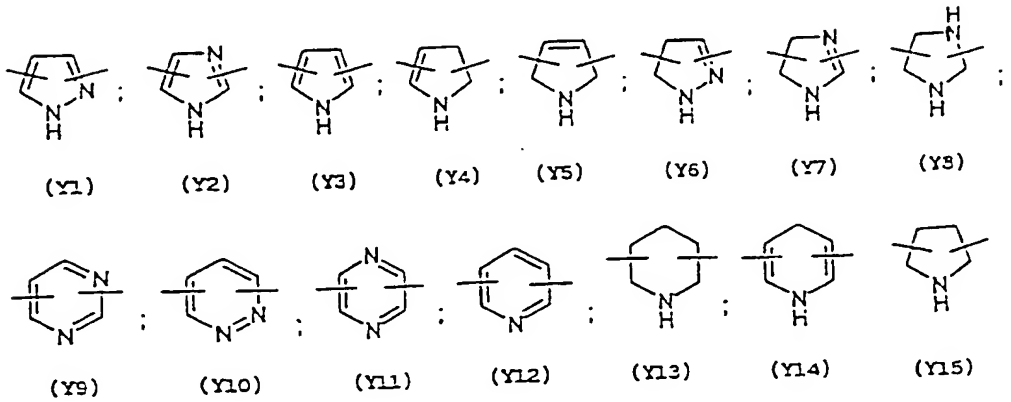
and R_{IVd} = H, R_{IVd1} is CH_3, X = O and X_1 is as above defined for Ia);

when R is selected from Group V,

- when R is the formula (II), R_{Vii} and R_{Vii-1} are H, and A = R;
- when R is the formula (X), A = RCO, t = 1 and u = 0;
- when R is the formula (XI), A = RCO, t = 1 and u = 0;
- when R is the formula (XIII), A = RCO, t = 1 and u = 0;
- when R corresponds to the formula (XXXX) or (XXXXI),

A= RCO, t = 1 and u = 0.

4. Salts according to claims 1-3, wherein Y in formula (B) of X_1 contains one or two nitrogen atoms in the ring and is selected from the following:



5. Salts according to claim 4, wherein the preferred radical Y of formula (B) of X_1 is Y12 (pyridyl) substituted in position 2 and 6.

6. Salts according to claims 1-5, wherein the organic acids are selected from the following: oxalic, tartaric, maleic, succinic, citric acids and the inorganic acids from nitric, hydrochloric, sulphoric, phosphoric acids.

7. Salts according to claims 1-6, wherein R in formula A = $R(COX_u)_t$ is selected among those of Group I) and Group IV).

8. Salts according to claims 1-7 for use as medicaments.

9. Use of salts according to claim 8 for the preparation of drugs having an aniinflammatory activity.

10. Use of salts according to claim 8 for the preparation of drugs for the antithrombotic therapy.

11. Use of salts according to claim 8 for the preparation of drugs having an analgesic activity.

12. Use of salts according to claim 8 for the preparation of drugs for the septic shock therapy.

13. Pharmaceutical formulations for oral and parenteral use containing as active principles the salts of claims 1-7.

14. Compounds of formula

$$A - X_1 - N(O)_z$$

according to claims 1-8.